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David Phillips

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ALSTON & BIRD LLP

BANK OF AMERICA PLAZA

101 SOUTH TRYON STREET, SUITE 4000

CHARLOTTE, NC 28280-4000

EXAMINER

EMCH, GREGORY S

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/755,545	Applicant(s) PHILLIPS ET AL.	
	Examiner Gregory S. Emch	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 September 2008 and 18 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 21-23 and 50-52 is/are pending in the application.
- 4a) Of the above claim(s) 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 21, 22 and 50-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 18 August 2008 has been entered.

Response to Amendment

Claims 1 and 50-52 have been amended, and claims have been cancelled as requested in the amendment filed on 18 August 2008. Following the amendment, claims 1-5, 21-23 and 50-52 are pending in the instant application.

Claim 23 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in Paper filed on 09 March 2007.

Claims 1-5, 21, 22 and 50-52 are under examination in the instant office action.

Withdrawn Rejections

The rejection of claims 6, 7 and 13 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,470,826 is withdrawn as moot in response to the cancellation of said claims.

The provisional rejection of claims 1-7, 13, 21 and 22 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 87 of copending Application No. 10/318,283 is withdrawn in view of the abandonment of the '283 application.

The provisional rejection of claims 6, 7 and 13 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 60 of copending Application No. 10/575,049 is withdrawn as moot in response to the cancellation of said claims.

The provisional rejection of claims 6, 7 and 13 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51 and 57-60 of copending Application No. 10/571,837 is withdrawn as moot in response to the cancellation of said claims.

The rejection of claims 6, 7 and 13 under 35 U.S.C. 112, second paragraph is withdrawn as moot in response to the cancellation of said claims.

The rejection of claims 6 and 13 under 35 U.S.C. 103(a) as being unpatentable over WO 01/05998 to Duan et al. is withdrawn as moot in response to the cancellation of said claims.

The rejection of claims 6, 7 and 13 under 35 U.S.C. 103(a) as being unpatentable over WO 99/10364 A1 to Ruben et al. is withdrawn as moot in response to the cancellation of said claims.

The rejection of claim 13 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,041,538 to Ling et al. is withdrawn as moot in response to the cancellation of said claim.

New and remaining issues are set forth below.

Election/Restrictions

In the reply filed on 18 August 2008, Applicants state, "Claim 23 recites a method of preparing the pharmaceutical composition of claim 1. Claim 23 (Group XIX) was restricted from the claims of Group I. While the Examiner has made the restriction between Group I and Group XIX final, upon allowance of the elected product claims in Group I, the withdrawn process claims of Group XIX should be considered for rejoinder as outlined in MPEP 821.04(b). Upon rejoinder of claims directed to a previously nonelected process claims, the restriction requirement between the elected product of Group I and rejoined process of Group XIX will be withdrawn."

Applicants are advised that rejoinder will be considered upon a finding of allowability of the product claims. Applicants' attention is directed to MPEP 821.04, which states, "In order to be eligible for rejoinder, a claim to a nonelected invention must depend from or otherwise require all the limitations of an allowable claim. A withdrawn claim that does not require all the limitations of an allowable claim will not be rejoined.

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Furthermore, where restriction was required between a product and a process of making and/or using the product, and the product invention was elected and subsequently found allowable, all claims to a nonelected process invention must depend from or otherwise require all the limitations of an allowable claim for the claims directed to that process invention to be eligible for rejoinder. See MPEP § 821.04(b). In order to retain the right to rejoinder, applicant is advised that the claims to the nonelected invention(s) should be amended during prosecution to require the limitations of the elected invention. **Failure to do so may result in a loss of the right to rejoinder.”**

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 21, 22 and 50-52 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,470,826, in view of Kogure et al. (1995; citation 27 on IDS dated 30 August 2008).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '826 patent are directed to follistatin proteins and compositions thereof that additionally comprise a pharmaceutically acceptable carrier or diluent, as in the instant claims. Moreover, the Kogure et al. reference teaches a dosage of 1 μ g (i.e. 0.001 mg) of human follistatin in physiological saline administered to rats (p.1137, col.1, paragraph 3), which is in the dosage range recited by the instant claim 1. Furthermore, as stated previously, the dosage range of the claimed compositions is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize (see MPEP 2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal dosage of follistatin in the claimed composition. This would necessarily include provided increased dosages for larger animals (including humans) that weigh more than the rats treated in the Kogure et al. reference, as in claims 50-52. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of dosage would have been obvious at the time of Applicants' invention. Thus, the instant claims and those of the '826 patent are considered obvious variants.

In the reply filed on 18 August 2008 (regarding the previous obviousness double patenting rejection), Applicants state that the '826 patent is drawn to polypeptides exhibiting an inhibitory action over follitropin (i.e. follistatin polypeptides) and provides no information on formulating or for dosage amounts for the use of the polypeptides. Applicants assert that while a double patenting rejection is based solely on the disclosure of the claims, which in the instant case do not recite any dosage range, the specification itself is also silent as to possible dosage ranges. Applicants thus submit that a skilled person would not consider this citation as provide an enabling disclosure of a pharmaceutical composition providing a dosage of follistatin or a fragment(s) or analogue thereof, for the treatment or prevention of a disease associated with fibrosis or any other condition.

Applicants' arguments have been fully considered and are not found persuasive. It is noted that the instant rejection is in view of a secondary reference (the Kogure et al. reference), which provides further guidance for a selection of a dosage of the claimed follistatin compositions. Thus, whether or not the '826 patent is an enabling disclosure of a pharmaceutical composition providing a dosage of follistatin or a fragment(s) or analogue thereof is irrelevant to the instant rejection. Regardless, working examples are not required for anticipation. Moreover, the instant claimed limitation of "a pharmaceutical composition for the treatment and/or prophylaxis of disease associated with fibrosis in a vertebrate" (as recited by independent claim 1) is given no patentable

weight, as it is recited in the preamble and thus imparts no patentable weight on the claim (see MPEP § 2111.02, section II).

In the reply filed on 18 August 2008, Applicants assert that the dosage rates and formulations are not subject to mere optimization and would not be obvious to a skilled person, especially given the complexity when dealing with patients that have liver disease. Applicants assert that the attached article titled "Prescribing in Liver Disease", by Pirmohamed, M. (2006) Medicine 35:1, pages 31-34 (Appendix A) makes it clear that determining dosage rates for subjects with liver disease is far from straight forward.

Applicants' arguments have been fully considered and are not found persuasive. It is noted that the reference submitted as Appendix A has been considered only to the extent that it is relied upon to support Applicants' arguments, but will not be fully considered as regards all issues of patentability, and will not appear on the face of the patent resulting from the instant application, unless a proper IDS is filed (See 37 CFR § 1.97 and 1.98). Regarding said reference, it indeed teaches that dosage rates and choice of drug for treatment of liver disease would be factors that one of skill in the art (i.e. a clinician) would optimize. See the abstract of the reference which teaches "If a drug is needed for a patient with liver disease, the choice of drug, its dose, and duration of therapy must be carefully considered in order to avoid adverse effects. Ideally, in patients with liver disease, it is better to choose a drug that has a large therapeutic index, is largely devoid of pharmacokinetic and pharmacodynamic interactions, is devoid of hepatotoxic effects and is renally eliminated. However, the ideal drug with these properties is often not available, and in such cases, the dose and drug should be

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individualized to the patient, who should then be carefully monitored, and the drug used for the shortest period possible.” This is interpreted by the Examiner as optimization of parameters that is well within the level of skill in the art. Regardless, the current claims are drawn to compositions that are not limited to treatment of liver disease. Additionally, as stated previously, absent some demonstration of unexpected results from the claimed parameters, this optimization of dosage would have been obvious at the time of Applicants’ invention. Accordingly, Appendix A does not establish unexpected results to support non-obviousness of the dosage of the claimed compositions.

The provisional rejection of claims 1-5, 21 and 22 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 60 of copending Application No. 10/575,049 is maintained for reasons of record and as set forth below. Further, claims 50-52 are also subject to the instant rejection.

The provisional rejection of claims 1-5, 21 and 22 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51 and 57-60 of copending Application No. 10/571,837 is maintained for reasons of record and as set forth below. Further, claims 50-52 are also subject to the instant rejection.

In the reply filed on 18 August 2008, Applicants arguments are largely identical to the arguments set forth in the reply filed on 04 December 2007. That is, Applicants re-assert that the instant rejections are improper because the present application and the co-pending applications are not commonly owned. Applicants assert that the present application has an earlier filing date of than the copending applications, and if issued

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into a patent would expire before the expiration date of a patent issuing from the conflicting applications. Thus, Applicants assert that there is no unjust patent term extension. Applicants admit that the present application and the copending applications share a common inventor. Applicants provide a discussion of double patenting form paragraphs provided in MPEP chapter 800, e.g., regarding potential rejections under 35 U.S.C. 102(e) or 102(e)/103(a). Applicants discuss the Create Act and state that the present application and the '049 and '837 applications are not subject to a joint research agreement as defined by The CREATE Act. Applicants assert that even if the rejections were proper, the Examiner should allow the earlier filed application to issue.

Applicants' arguments have been fully considered and are not found persuasive. Again, the Examiner is aware that the instant application has an earlier U.S. effective filing date than the cited copending applications, that the copending applications and the instant application are not currently commonly owned and that the copending applications and the instant application share a common inventor. The Examiner has used Chart I-B for conflicting claims between two applications provided in MPEP 804 in formulating the instant provisional double patenting rejections. Since the applications collectively share at least one common inventor but do not collectively share a common assignee, Chart I-B teaches that the Examiner should use form paragraphs 8.33 & 8.35 or 8.37 to provide a provisional obviousness double patenting rejection, which the Examiner has provided in the office action dated 04 June 2007. Thus, it is indeed proper to make and maintain a provisional obviousness-type double patenting rejection, even if the conflicting applications are not commonly owned. Since the instant

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application has the earliest U.S. effective filing date, no provisional rejections under 35 U.S.C. 102(e)/103(a) have been put on the record. Regarding Applicants' comment that the Examiner should allow the earlier filed application to issue without a terminal disclaimer, inasmuch as the current claims are not patentable at this time, the provisional obviousness-type double patenting rejections are properly maintained.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 21, 22 and 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to a pharmaceutical composition for the treatment and/or prophylaxis of disease associated with fibrosis in a vertebrate, said composition follistatin, or a fragment(s) or analogue thereof, wherein said composition is provided as a dosage form comprising from 0.001 mg to 5 mg of the follistatin.

The claimed compositions require either "follistatin, or a fragment(s) or analogue thereof;" however, the dosage ranges recited by the claims require dosages "comprising from [a dosage range] of the follistatin." Thus, it is unclear whether the claims must encompass follistatin (because the dosage is for follistatin only) even if they encompass a fragment or analogue thereof. The former limitation refers to follistatin, or a

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fragment(s) or analogue in the alternative; however, the latter limitation requires a certain amount of follistatin itself.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kogure et al. (1995; citation 27 on IDS dated 30 August 2008).

The claims are directed to a pharmaceutical composition for the treatment and/or prophylaxis of disease associated with fibrosis in a vertebrate, said composition follistatin, or a fragment(s) or analogue thereof, wherein said composition is provided as a dosage form comprising from 0.001 mg to 5 mg of the follistatin.

The Kogure et al. reference teaches a dosage of 1 µg (i.e. 0.001 mg) of human follistatin diluted in physiological saline as administered to rats, which accelerated liver regeneration in these partially hepatectomized rats (abstract and p.1137, col.1, paragraph 3). As stated above, the instant claimed limitation "a pharmaceutical composition for the treatment and/or prophylaxis of disease associated with fibrosis in a vertebrate" is recited in the preamble and thus imparts no patentable weight on the claim (see MPEP § 2111.02, section II). Thus, since the Kogure et al. reference

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teaches a follistatin composition comprising follistatin at 0.001 mg and a pharmaceutically carrier (physiological saline), the reference meets the limitations of claims 1, 2, 5, 21 and 22.

Claim 3 requires that the follistatin is a single chain protein comprising between 288 and 315 amino acids with a molecular weight of between about 30,000 and 60,000 Daltons as estimated by SDS-PAGE in the absence of reducing agents, derived from follicular fluid and able to inhibit the secretion of follicle-stimulating hormone (FSH). These limitations are inherently met by the Kogure et al. reference, since the limitations are simply describing properties of human follistatin, as evidenced by the instant specification and sequence listing. Therefore, since the Kogure et al. reference teaches human follistatin, the reference meets the limitations of claim 3 (both expressly and inherently). Applicants are reminded that chemical compounds and their properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA1963)), as are their processes and yields (*In re Von Schickh*, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)).

Since the reference teaches all the elements of the claims, claims 1-3, 5, 21 and 22 are anticipated by Kogure et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kogure et al. (1995; citation 27 on IDS dated 30 August 2008).

The claims are directed to a pharmaceutical composition as set forth above, wherein the dosage form comprises from 0.01mg to 5 mg of follistatin (claim 50), wherein the dosage form comprises from 0.01mg to 2 mg of follistatin (claim 51), and wherein the dosage form comprises from 0.1mg to 1 mg of follistatin (claim 52)

The Kogure et al. reference teaches as set forth above. The difference between the disclosure of the Kogure et al. reference and the claimed invention is that the Kogure et al. reference does not teach the dosage ranges recited by claims 50-52. However, as set forth above, the dosage range of the claimed compositions is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize (see MPEP 2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal dosage of follistatin in the claimed composition. This would necessarily include providing increased dosages for animals (including humans) that weigh more than the rats treated in the Kogure et al. reference. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of dosage would have been obvious at the time of Applicants' invention. Furthermore, it would have been reasonable to predict that the claimed compositions could have been successfully produced as providing alternative dosages for larger animals, including humans. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve Kogure et al.'s compositions with optimization methods to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. Such would amount to substitution of known equivalents to obtain predictable results. Thus, claims 50-52 are unpatentable over the Kogure et al. reference.

The rejection of claims 1, 2, 4, 5, 21 and 50-52 under 35 U.S.C. 103(a) as being unpatentable over WO 01/05998 to Duan et al. is maintained for reasons of record and as set forth below. Furthermore, claims 3 and 22 are also subject to the instant rejection under 35 U.S.C. 103(a).

The rejection of claims 1, 2, 5, 21, 22 and 50-52 under 35 U.S.C. 103(a) as being unpatentable over WO 99/10364 A1 to Ruben et al. is maintained for reasons of record and as set forth below.

In the reply filed on 18 August 2008, Applicants address both rejections collectively. Applicants assert that both WO01/05998 and WO99/10364 discuss methods of use for follistatin-3. Applicants assert that follistatin-3 is a follistatin-related protein [FSTL3], also known as follistatin-related protein [FSRP] (and does have a sequence as shown in SEQ ID NO: 2), which is different in its physical, chemical and physiological properties to follistatin. Applicants assert that the encoding gene is also known as FST-related gene [FLRG] and that the claims as currently amended recite specific pharmaceutical compositions employing follistatin or fragments or analogues thereof. Applicants assert that the FSTL3 protein is structurally and functionally different from follistatin and assert that each is a unique protein which has its own unique roles as demonstrated when the gene for each protein is knocked out, as evidenced by Appendix B (the Matzuk et al. reference) and Appendix C (the Mukherjee et al. reference). Applicants assert that Appendix D (the Sidis et al. reference) teaches that follistatin and FSTL3 have several distinctions, e.g. FSTL3 does not have a heparin binding site and is a weak agonist of activin.

Applicants' arguments have been fully considered and are not found persuasive. It is noted that the references submitted as Appendix B, Appendix C and Appendix D have been considered only to the extent that they are relied upon to support Applicants' arguments, but will not be fully considered as regards all issues of patentability, and will not appear on the face of the patent resulting from the instant application, unless a proper IDS is filed (See 37 CFR § 1.97 and 1.98). As Applicants have pointed out, the claims recite specific pharmaceutical compositions employing follistatin or fragments or analogues thereof. Thus, Applicants' arguments regarding follistatin-3 being different from follistatin are not persuasive because this protein meets the claimed limitation of an analogue of follistatin. The specification defines the term "analogue" as referring to "a derivative of a target polypeptide comprising addition, deletion, or substitution of one or more amino acids, the analogue retaining, however, substantially the same function as the target polypeptide." (p.17, lines 6-14). Thus, as long as follistatin and FSTL3 have at least one function in common, the prior art references meet the limitations of the claims as evidenced by the definition in the instant specification. Accordingly, the Sidis et al. reference (Appendix D) teaches that follistatin and FSTL3 are both "activin-binding and neutralization proteins that also bind myostatin" and that "activin-binding affinities and kinetics were comparable between the [follistatin] isoforms and FSTL3." Thus, although there may be some differences between some functions of follistatin and FSTL3 as evidenced by Applicants' submitted references, both proteins share at least one common function, e.g. activin antagonism, which as set forth by Applicants' specification provides the therapeutic efficacy of the claimed compositions. In fact, the

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instant specification teaches that FSTL3 is one of the proteins preferred for the compositions of the invention (p.14, lines 13-20). Moreover, cancelled claims 6 and 7, which were dependent on independent claim 1 recited that the pharmaceutical composition can comprise FSTL3, providing further evidence that FSTL3 meets the claimed limitation of a follistatin analogue. Therefore, both the Duan et al. and the Ruben et al. references teach the claimed limitation of a follistatin analogue, since FSTL3 is taught therein. Regardless, as stated previously, the '998 document to Duan et al. also teaches a follistatin polypeptide that is 100% identical to the instant SEQ ID NO: 1, and fragments, analogues and derivatives thereof, as in the instant claims. Thus, in addition to FSTL3, the Duan et al. reference teaches the human follistatin protein itself.

In the reply filed on 18 August 2008, Applicants assert that neither of the cited references teaches, explicitly or implicitly, a pharmaceutical composition comprising a dosage form comprising 0.001 mg to 5mg of follistatin, as recited in the claims.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above, it would have been customary for an artisan of ordinary skill to determine the optimal dosage of follistatin in the claimed composition. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of dosage would have been obvious at the time of Applicants' invention.

In the reply filed on 18 August 2008, Applicants assert that conditions associated with fibrosis are typically accompanied or preceded by inflammation causing cell death by necrosis and this complex process requires the involvement of many cell types both

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within the tissue or organ concerned, but also involves the invasion of the damaged tissue by components of blood-borne cells such as leucocytes, together with exposure to a variety of compounds that form part of the organism's inflammatory response e.g. many cytokines that are produced in a highly coordinated manner. Consequently, Applicants assert that the prophetic uses of follistatin-3 espoused in documents WO 99/10364 and WO 01/05998, or the doses to be used in such uses could not be predicted by a skilled person at the date of those documents, as the uses are speculative, being unsupported by *in vivo* experimental data, or even experimental data relating to treatment of conditions associated with fibrosis (or any other condition). Thus, Applicants assert that a skilled person, on reading either of these documents, would not have considered using follistatin in place of follistatin-3, would not have considered the use of follistatin-3 for treatment of any condition, including conditions associated with fibrosis, and would not have been provided with any useful information towards dosing of follistatin, or even follistatin-3.

Applicants' arguments have been fully considered and are not found persuasive. Again, the claimed limitation of "a pharmaceutical composition for the treatment and/or prophylaxis of disease associated with fibrosis in a vertebrate" is recited in the preamble and thus imparts no patentable weight on the claim (see MPEP § 2111.02, section II). Thus, the limitations of "wherein the disease associated with fibrosis is one of: a hyperproliferative or inflammatory fibrotic disease; a pulmonary fibrosis; an inflammatory bowel disease, or a related condition such as ulcerative colitis or Crohn's Disease; or liver fibrosis or cirrhosis" in claim 21 and "wherein the disease associated with fibrosis is

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liver fibrosis or cirrhosis” in claim 22 are also given no patentable weight. Thus, Applicants' assertions regarding the prior art references of record as not providing data relating to the treatment of a condition are actually irrelevant. Moreover, working examples are not required for anticipation. Regardless, the arguments immediately set forth above cannot be accepted since the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Regarding claim 3, said claim is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/05998 to Duan et al. because said claim requires that the follistatin is a single chain protein comprising between 288 and 315 amino acids with a molecular weight of between about 30,000 and 60,000 Daltons as estimated by SDS-PAGE in the absence of reducing agents, derived from follicular fluid and able to inhibit the secretion of follicle-stimulating hormone (FSH). This limitation is inherently met by the Duan et al. reference, since the claim is simply describing human follistatin, as evidenced by the instant specification and sequence listing. Therefore, since the Duan et al. reference teaches human follistatin, i.e. a follistatin polypeptide that is 100% identical to the instant SEQ ID NO: 1 (as evidenced by Sequence alignment A, of record), the reference teaches the dependent limitations of claim 3. Applicants are reminded that chemical compounds and their properties are inseparable (In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA1963)), as are their processes and yields (In re Von Schickh, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)).

To clarify the record regarding claim 22, although the merits of this claim as being unpatentable over the Duan et al. reference was set forth on p.10 of the office action dated 20 March 2008, the claim was inadvertently omitted from the first line of the rejection set forth on p.9 of the office action dated 20 March 2008.

The rejection of claims 1, 2, 3, 5, 21, 22 and 50-52 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,041,538 to Ling et al. is maintained for reasons of record and as set forth below.

In the reply filed on 18 August 2008, Applicants assert that the prophetic therapeutic uses and suggested dosage rates are not supported by any *in vivo* or even *in vitro* studies, and therefore the comments above (in relation to documents WO 99/10364 and WO 01/05998) are equally applicable here. Applicants assert that a skilled person would not consider this citation to provide an enabling disclosure of a pharmaceutical composition providing a dosage of follistatin or a fragment(s) or analogue thereof, for the treatment or prevention of a disease associated with fibrosis or any other condition.

Applicants' arguments have been fully considered and are not found persuasive. The claimed limitation of "a pharmaceutical composition for the treatment and/or prophylaxis of disease associated with fibrosis in a vertebrate" is recited in the preamble and thus imparts no patentable weight on the claim (see MPEP § 2111.02, section II). Thus, the limitations of "wherein the disease associated with fibrosis is one of: a hyperproliferative or inflammatory fibrotic disease; a pulmonary fibrosis; an inflammatory

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bowel disease, or a related condition such as ulcerative colitis or Crohn's Disease; or liver fibrosis or cirrhosis" in claim 21 and "wherein the disease associated with fibrosis is liver fibrosis or cirrhosis" in claim 22 are also given no patentable weight. Thus, Applicants' assertions regarding the prior art references of record as not providing data relating to the treatment of a condition are irrelevant.

In the reply filed on 18 August 2008, Applicants assert that while the suggested dose range of from about 0.1 to about 1 mg per kg of body weight for administration on a regular basis as a male contraceptive taught by the '538 patent, Applicants assert that this is far too high a dosage rate for the use of follistatin to regulate fibrosis. Applicants assert that the claims have been amended to recite a pharmaceutical compositions wherein the compositions are provided as dosage forms comprising from 0.001 mg to 5mg of follistatin (or narrower ranges). Applicants assert that even at the lowest dosage rate considered by the '538 patent (0.1mg/kg body weight), an average person of from 60-75kg would require at least 6 to 7.5mg.

Applicants' arguments have been fully considered and are not found persuasive. Indeed, at col.12, lines 16-21, the '538 patent teaches a dosage range for follistatin of 0.1 to about 1 mg per kg of body weight. Applicants' assertion that this is far too high a dosage rate for the use of follistatin to regulate fibrosis is irrelevant because regulating fibrosis is not required by the claims (as set forth repeatedly above). Applicants' assertion that an average person of from 60-75kg would require at least 6 to 7.5mg is irrelevant as the patent disclosure is not limited to administration to average persons. The skilled artisan would indeed be motivated to use the dosages encompassed by the

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claims for treatment of individuals that weigh less than 60-75kg. It is noted that many of these proteins can be formulated to treat animals, e.g. pets or experimental animals. If the artisan used the teachings in the '538 patent to treat a cat, for example, the artisan would most likely use a dosage range as recited in the claims. The instant claims do not require human treatment and the disclosure of the '538 patent is also not limited to humans.

In the reply filed on 18 August 2008, Applicants assert that dosage rates and formulations are not subject to mere optimization and would not be obvious to a skilled person, especially given the complexity when dealing with patients that have liver disease. Applicants again point to the Pirmohamed reference to allegedly support this stance.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above, the Pirmohamed reference (Appendix A) indeed teaches that dosage rates and choice of drug for treatment of liver disease would be factors that one of skill in the art (i.e. a clinician) would optimize. See the abstract of the reference which teaches "If a drug is needed for a patient with liver disease, the choice of drug, its dose, and duration of therapy must be carefully considered in order to avoid adverse effects. Ideally, in patients with liver disease, it is better to choose a drug that has a large therapeutic index, is largely devoid of pharmacokinetic and pharmacodynamic interactions, is devoid of hepatotoxic effects and is renally eliminated. However, the ideal drug with these properties is often not available, and in such cases, the dose and drug should be individualized to the patient, who should then be carefully monitored,

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and the drug used for the shortest period possible.” This is interpreted by the Examiner as optimization of parameters that is well within the level of skill in the art. Regardless, the current claims are drawn to compositions that are not limited to treatment of liver disease. Additionally, as stated previously, absent some demonstration of unexpected results from the claimed parameters, this optimization of dosage would have been obvious at the time of Applicants’ invention. Accordingly, Appendix A does not establish unexpected results to support non-obviousness of the dosage of the claimed compositions.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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/G.E./

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
04 December 2008

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646